CELLULAR ACIDIFICATION AS A NEW APPROACH TO CANCER TREATMENT AND TO THE UNDERSTANDING AND THERAPEUTICS OF NEURODEGENERATIVE DISEASES

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Abstract

During the last few years, the understanding of the dysregulated hydrogen ion dynamics and reversed proton gradient of cancer cells has resulted in a new and integral pH-centric paradigm in oncology, a translational model embracing from cancer etiopathogenesis to treatment. The abnormalities of intracellular alkalinization along with extracellular acidification of all types of solid tumors and leukemic cells have never been described in any other disease and now appear to be a specific hallmark of malignancy. As a consequence of this intracellular acid-base homeostatic failure, the attempt to induce cellular acidification using proton transport inhibitors and other intracellular acidifiers of different origins is becoming a new therapeutic concept and selective target of cancer treatment, both as a metabolic mediator of apoptosis and in the overcoming of multiple drug resistance (MDR). Importantly, there is increasing data showing that different ion channels contribute to mediate significant aspects of cancer pH regulation and etiopathogenesis. Finally, we discuss the extension of this new pH-centric oncological paradigm into the opposite metabolic and homeostatic acid-base situation found in human neurodegenerative diseases (HNDDs), which opens novel concepts in the prevention and treatment of HNDDs through the utilization of a cohort of neural and non-neural derived hormones and human growth factors.

Introduction. A brief historical account of cancer-related homeostasis.

In the 1920´s, Claude Bernard had created the philosophical and physiological concept of the *milieu interieur* [1, 2]. Walter Cannon followed with a similar idea and terminology to initiate the first studies on homeostasis. From these seminal considerations the concept of homeostasis was extended to include acid-base homeostasis [3]. These precedents inspired Hans Selye to create his famous General Adaptation Syndrome [4]. While the term homeostasis initially referred to a balanced, dynamic and systemic physiological situation, the term allostasis refers to multiple interactions between the body and cellular systems to maintain a physiological stability, given that some of those systems can become overactived or dysregulated [5, 6]. These classical medical visions, that considered all body systems and the organism as a whole, inspired our interest on how the hierarchical organization of physiopathological acid-base systemic deviations could be applied to cancer biology. In that vein, we initially referred to the cancer situation as a "chronic anti-adaptation syndrome", a parallel concept of allostasis [7], and showed the existence of a systemic alkalotic acid-base deviation of the blood of patients with different solid tumors [8].

During the last few years and after one hundred years of metabolic cancer research following the seminal findings of Otto Warburg [9], there has been a fast and growing interest on the dysregulation of proton [H^+]-related mechanisms, which underlie the initiation and progression of the neoplastic process [10-17]. This new pH-centric paradigm of cancer is based upon the fact that all cancer cells and tissues have a pivotal energetic and homeostatic/allostatic disturbance of their metabolism that is completely different from all normal tissues. This is an aberrant regulation of hydrogen ion dynamics leading to a reversal of the normal intracellular/extracellular pH gradient (↑pHi/↓pHe, or "proton gradient reversal", PGR) [18, 19], where malignant intracellular alkalinization has become a selective and specific hallmark of cancer intracellular homeostatic failure, in both solid tumors and leukemias, since it has not been described in any other disease process [18].

This PGR of the cancer cell is associated with the origin of the malignant process and with cellular transformation, proliferation, local growth, motility, migration, activation

of the metastatic process, resistance to chemotherapy and with the phenomenon of the spontaneous regression of cancer [18, 20]. Therefore, measuring intracellular pH (pHi) in tumors seemed to be essential for the monitoring of cancer progression and the response of cancer cells to various treatments. This is why new methods to determine pHi in tumors have been developed [21]. On the other hand, attempts to control and reverse the extracellular/intratumoral acidification have been thought to represent a viable therapeutic approach to control tumor growth and the metastatic process. To this end, proton pump V-ATPase inhibitors (PPI) were initially proposed and have been later used in preclinical and clinical studies, but not always succesfully when associated to chemotherapy [20, 22-27], as well as in the overcoming of resistance to certain chemotherapeutic drugs [23]. Also, the utilization of alkaline diets using bicarbonate or other buffer infusions have been tried but proved not to be feasible in bedside oncology, either because toxicity or lack of effect [28, 29]. These studies illustrate why it is important to take into account that tumor interstitial acidity is a consequence of a pathological induction of intracellular alkalinity as a result of proton transport extrusion driven by up-regulation of one or more of membrane-bound proton transporters (PT) [9]. This is the reason why we support a more etiological, and thus radical therapeutic approach rather than struggling directly against the extracellular acidification of malignant tumors, which at the most it will be a collateral and beneficial side-effect of this new pH-centric approach to cancer treatment. The idea is to induce a selective intracellular acidification of cancer cells by blocking acid extrusion through the utilization of pharmacological dosages of a cohort of proton transport inhibitors (PTIs) [30] and/or other non PT-derived cell acidifiers with known anticancer properties (see later sections). Furthermore, PTIs would decrease the extracellular/intratumoral acidification of malignant tumors and reverse the tumor-selective malignant PGR known to stimulate local invasion and the metastatic process. Thus, intracellular acidification becomes fundamental in any attempt to induce a selective apoptosis of malignant cells [31-34]. In this review, we will analyze the different classes of anticancer drugs currently available to induce cellular acidification as a new approach to the treatment of cancer.

Ion channels as a transversal bridge between oncology and research into neurodegeneration.

Ion channels contribute in the mediation of important aspects of both cancer and neurodegeneration, among which pH regulation is a fundamental one. This makes the knowledge of ion channel physiopathology a useful tool for bridging research between oncology and neurology. Its study also permits the translation of the pH-centric paradigm from the cancer field to some fundamental aspects of the etiopathogenesis and treatment of human neurodegenerative diseases (HNDDs). This widening of perspective from oncology to HNDDs is developed here as an attempt to embrace two otherwise widely separated areas of research within one encompassing and integrated vision *(transversal research)* [35]. This new approach is based upon the fact that these two situations are apparently opposite regarding cellular acid-base and H^+-related cellular homeostatic balance: an alkaline pHi that occurs in malignancy (high pHi-mediated anti-apoptosis or *pathological anti-apoptosis*) while an acidic pHi occurs in certain HNDDs like Alzheimer's disease (AD) (low pHi-mediated "spontaneous" apoptosis or *pathological apoptosis*) (Table 1) [35-39]. Therefore, on the basis of the dynamics of the hydrogen ion (H^+) both situations belong to opposite ends of a metabolic spectrum that determine the fate of cells in cancer and HNDDs. Finally, this integrated

homeostatic perspective can also open novel strategies for the prevention and treatment of HNDDs through the use of a cohort of human growth factors (hGF) and hormones that increase pHi and stimulate cellular metabolism by activating some of the alkalizing proton transporters, mainly the Na^+/H^+ exchanger (NHE), that are over-expressed or over-activated in cancer **(Figure 1)**.

Rationale. Proton transport and pH dynamics as an approach to cancer etiopathogenesis and treatment.

The primary phenomenon that leads to a reversed hydrogen ion gradient in cancer metabolism is the pathological regulation of hydrogen ion dynamics of malignant cells and tissues (↑pHi/↓pHe) [11, 18, 19, 40] (Table 1). Seminal research in this area first demonstrated that the stimulation of the Na^+-H^+ exchanger isoform 1 (NHE1) was fundamental to oncogene-driven neoplastic transformation. The activation of NHE1 stimulates proton extrusion with a resultant intracellular alkalinization and extracellular acidification [41]. This cytosolic alkalinization was shown to be the primary driver of a series of transformation hallmarks, namely, increased growth rate, substrate-independent growth, growth factor independence and glycolysis in aerobic conditions and tumor growth [41, 42]. In addition, it has been demonstrated that some oncogenes utilize NHE1-induced alkalinization to induce the cancer specific pH dysregulation of cancer cells [19, 43]. However, from pH-driven transformation to tumor growth and metastatic progression in different malignant tumors can also be mediated by the overexpression and/or overactivation of other PTs like monocarboxylate transporters (MCTs) [44-51].

In the same vein, a direct cause-effect relationship between the elevation of pHi in cancer and the multiple drug resistance (MDR) phenotype has also been described by different research groups [52-56]. Indeed, the failure to kill tumor cells following chemotherapeutic treatment appears to be highly dependent on their resistance to undergo intracellular acidification, a situation that is apparently necessary as a prior condition that forces cancer cells to engage in a tumor-specific apoptotic or para-apoptotic processes [31, 33, 57]. This is part of the defensive anti-apoptosis strategy of all types of cancer ("the neostrategy of cancer cells and tissues") [18], known to be mediated by multiple and different cellular anti-acidifying mechanisms [53, 58-60].

Recently, it has been demonstrated that H^+ efflux alone is sufficient to induce dysplasia and potentiate growth and invasion by oncogenic Ras and, furthermore, that inhibiting this H^+ efflux produced cell death in invasive primary tumor cell lines that was related to a secondary mitochondrial depolarization [61]. Similar results have been obtained by the group of Fliegel, showing that NHE-mediated H^+ extrusion by itself has a carcinogenic effect on breast cells [62, 63]. In these studies, NHE1 hyperactivity appears to be an early and decisive driver in breast cancer carcinogenesis [42]. Furthermore, an increased pHi and increased proton efflux with a secondary acidified microenvironment has been implicated in the transition and progression from precancerous ductal carcinoma *in situ* to invasive breast cancer, with the precancerous lesion already showing a higher than normal proton export rate [64]. We agree with the conclusion that H^+ efflux is the main and final cause of breast cancer, independently of the many other mediating factors that can be involved in the development of this cancer. Moreover, this seems primary to the fact that a very acidic extracellular microenvironment secondary to proton transporters (PTs)-mediated H^+ efflux is known to be a specific hallmark of all malignant tumors [11, 12, 19, 61, 65]. In these very hostile conditions, cancer cells of all tissue origins and showing different genetic

alterations defend themselves from highly toxic microenvironment by activating H^+ efflux through a series of proton pumps, exchangers and transporters [11, 19, 22, 66]. Thus, the induction of a selective intracellular acidification of cancer cells with PTIs and/or PPIs [22] in-order-to block different PTs, either singly [67-70] or simultaneously [30], and/or with other cell acidifying molecules of different origins and natures is increasingly becoming a promising choice in a new and different attitude towards modern cancer chemotherapeutics [9, 13, 33, 71-76].

Searching for universal root-mediating mechanisms of pH-related carcinogenesis.

A cancer-specific intracellular alkalosis represents a common final pathway in cell transformation and an anti-apoptotic defensive mechanism in cancer cells. This has been demonstrated to be induced by a myriad of factors. These include the overexpression/hyperactivity of different PTs apart from NHE [11, 19, 49, 51, 77-84] and PPs [85], the MDR promoting effects of certain oncogenes, virus and viral proteins, gene products, like Bcl-2 [58, 86], a dysfunctional p53, various growth and/or trophic factors (GFs) [87-91] and a number of chemical carcinogens. Other carcinogenic NHE-related factors are chronic hypoxia and hypoxia-inducible factor (HIF) [66, 92], different hormones and even high glucose loads [93] (Table 2 and Figure 1).

Importantly, if a myriad of unrelated factors coming from many different origins and natures are carcinogenic, we are constrained to hypothesize that the hyperactivity of NHE1 and its pHi raising ability, as well as the overexpression of other PTs, may constitute a general phenomenon that can perhaps be extended to many other unidentified carcinogenic factors. This seems to suggest "a universality of phenomenon involved in human carcinogenesis" (Table 2) [41, 58, 59, 87-89, 94-98]. Or, in other words, as Otto Warburg wrote concerning his famous, however controversial, "damaged respiration" theory [99] on the primary cause and origin of cancer*:* "there are uncountable secondary causes: almost everything causes cancer, even time" [100, 101]. This statement by Warburg saying that even "time" causes cancer seems to be confirmed by recent research showing that NHE activity increases during ageing in humans [102]. Finally, environmental acidification, mediated by overexpression of either NHE and/or other PTs, is known to play a role in hindering DNA repair, increasing mutagenesis and driving genomic instability in cancer [103-111]. Thus, the acidic pHe role in genomic instability can be considered as the last step in closing the vicious cycle of a single and multidimensional process ending up in a very dynamic and highly self-organized chaos (*"the neostrategy of cancer cells and tissues*") [9, 18].

Incidentally, some recent reviews on environmental carcinogenesis have not taken into consideration this association between pH/NHE1/PTs and environmental carcinogenesis [112, 113]. However, other groups have paid close attention to these observations [96]. Finally, DNA damage has also been associated with NHE1 expression, intracellular alkalinization and Bcl-xl deamidation, this preceding apoptosis in different tumor cell lines. No matter that this may seem to be a paradox at first sight, since cell alkalinization has rarely been associated with apoptosis [114], this association can also help to link the new pH-centric paradigm with the classical DNA-paradigm in cancer research and treatment.

Going after NHE1: further along the new anticancer road.

Indeed, as described above, it is well established that there is an increased expression and/or activity of one or more of the pH regulators in most or all cancer cells of different origins [19, 46, 72, 115, 116]. Among all the known pH regulators, the Na^+/H^+ exchanger type 1 (NHE1) has drawn a lot of attention because not only it is overexpressed but also over-activated in many kinds of cancer cells, from breast to ovary [42, 63, 65, 117, 118]. Besides, its hyperactivity is associated with cancer cell survival, migration, invasion and metastatic progression [65, 119]. NHE1 catalyzes the electroneutral exchange of H^+ and Na^+, driven by the inwardly directed electrochemical Na^+ gradient [120], and it is ubiquitously expressed at the plasma membrane of all mammalian cells. It is considered to be a "house-keeping" intracellular H^+ regulator, protecting normal cells from intracellular acidification [121]. NHE1 is quiescent at physiological pHi (pHi $\geq$ 7.2), but its activity increases rapidly upon intracellular acidification following a dimeric Monod-Wyman-Changeux cooperative mechanism [122]. Its activity is tightly regulated and its sensitivity to pHi is increased in situations that can be found in the context of cancer, such as when it is activated by growth factors, hormones, different mitogens and environmental carcinogens [123-125] (Figure 1). Finally, it is also involved in cancer cell motility and matrix degradation [126, 127] despite a relatively low alkalinized pHi [65]. For all these reasons, during the last few years NHE1 has become a very important target in selective cancer therapeutics [9, 67, 71, 86, 115, 128-131]. Most recently, inhibition of NHE1 and cancer proton reversal have been correctly regarded as the latest concept in cancer treatment [22, 30, 51, 132, 133].

Anticancer and other diseases potential of the new and potent NHE inhibitors. Cellular acidification and apoptosis.

Decreasing NHE1 expression or inhibiting its activity leads to hyperacidification of the intracellular space, inhibition of glycolysis, tumor cell growth arrest and selective apoptosis [33, 134, 135]. Indeed, it has been shown that cariporide (CP, HOE 642), a selective and potent NHE1 inhibitor, reduces proliferation and induces apoptosis through a decrease of intracellular pH and induces apoptosis in cholangiocarcinoma cells [136]. While intracellular acidification inhibits the expression of vasoendothelial growth factor (VEGF) when NHE is inhibited [137], cariporide also inhibits angiogenesis and the growth of leukemia cells by inhibiting the Na^+/H^+ exchanger, [138]. Cariporide has also been proved to be useful in overcoming metastatic progression and multiple drug resistance (MDR) [139].

Furthermore, in combination with inhibitors of the Na^+-dependent Ca^{2+} transporter, cariporide induces a non-apoptotic death in glioma cells [140]. In the same line, cariporide acts synergistically with erlotinib in reducing growth and invasion of pancreatic ductal adenocarcinoma (PDAC) [141]. Regarding cariporide, it is most surprising that it has not raised any interest to facilitate its preclinical and/or translational research in the field of oncology, more if its international patent literally reports that "there is a surprising prolongation of life of cancer in the elderly to an extent which has to date been achievable by no other group of drugs or by any natural products. This is a unique effect of NHE inhibitors like cariporide (CARIPORIDE PATENT WO2004007480, SANOFI-AVENTIS, 2005).

Importantly too, the 5-aryl-4-(4-(5-methyl-1*H*-imidazol-4-yl) piperididn-1-yl) pyrimidine analog (compound 9t) was reported to be 500-fold more potent against

NHE1 than cariporide and to have a greater selectivity for NHE1 over NHE2 (1400-fold) [142]. Additionally, compound 9t is orally bioavailable, has low side effects in mice and shows a significantly improved safety profile over other NHE1 inhibitors (BRISTOL-MYERS SQUIB PATENT WO 01 27107 A2, PCT/US00/27, 2001,US 6887870 B1; EP 1224183 B1). Surprisingly too, this drug has never been tested as an anticancer drug to date and, somehow, has been lost "missing in inaction" due to a lack of further interest by the discoverers and/or patent holders concerning its possible utilization in preclinical and/or clinical oncology and in spite of its most promising antitumoral characteristics and selective anticancer potential.

Another potent and selective NHE1 inhibitor, the aminophenoxazine derivative Phx-3, has been shown to trigger apoptosis in a variety of cancer cell lines. In animal models, Phx-3, effectively and without noticeable toxicity reversed tumor growth after subcutaneous injection of adult leukemia cells [31, 57]. In any case, these new and selective NHE1 inhibitors show a great potential to become potent anticancer agents in preclinical trials and, eventually, in cancer patients. At the present time, research along this line in different malignancies shows that several PTs and their inhibitors are very selective as diagnostic, predictive and potential anticancer agents [54, 69, 143].

On the contrary, while decreasing intracellular pH induces a cell death program (CDP), apoptotic, para-apoptotic or necrotic, in malignant cells, the elevation of cellular pH by different methods protects cancer cells by preventing them from entering the apoptotic cascade. In this case too, this suggests a universality of phenomenon concerning the role of pH in cell fate [144]. Interestingly, clinical trials using the new NHE inhibitor rimeporide are being conducted in neuromuscular processes like Duchenne Muscular Dysthropy, the only disease outside the cancer context where a high pHi has been shown to be involved in its pathogenesis [145, 146]. In terms of mechanisms, it is known that decreasing intracellular pH induces a cell death program, either via apoptosis, para-apoptosis or necrosis, while the elevation of cellular pH by different methods protects cancer cells by preventing them from entering the apoptotic cascade. On the low pHi therapeutic-apoptotic side, striking results in leukemia cells were initially reported with the amiloride derivative and potent NHE1 inhibitor 5-(*N*,*N*-hexamethylene) amiloride (HMA). This compound decreases the pHi below the survival threshold leading to selective apoptosis in a variety of human leukemic cells [33]. An increasing number of later studies in the same line have led to the conclusion that inducing a low pHi-mediated apoptosis can be a cancer-specific therapeutic strategy for all cancer cells and tissues [13, 35, 62, 68, 69, 134, 137, 147-152]. Most recently, HMA has shown selective cytotoxicity to breast cancer cells irrespective of their molecular profile, proliferative status or species of origin, suggesting a necrotic cell death mechanism common to all mammary tumor subtypes [153]. Moreover, acting not only on NHE1 but also on other PTs leads to a significant control of malignant growth and tumor angiogenesis, also showing an important role in the overcoming of MDR [137, 138, 154-157]. The final aim should be to target the selective acid-base disruption of cancer cell metabolism based on the H^+-dependent thermodynamic advantages that malignant cells possess over their normal counterparts, in order to exploit such differences in selective cancer therapeutics.

Interestingly, Marches *et al*. elegantly showed the intimate link between cancer biochemistry, molecular biology and cancer-related immunity by demonstrating that the anti-IgM-mediated induction of cell death in human B lymphoma cells is dependent on NHE1 inhibition and subsequent intracellular acidification. This important publication conceptually unified three different fields of oncology research: biochemistry, molecular biology and cancer immunity under one wider embracing unit [52, 158]. The

concerted utilization of PTIs as a primary cancer treatment, as well as an adjuvant measure in overcoming MDR, has been advanced by our group in several publications approached from different perspectives, ranging from basic physics to bedside therapeutics [35, 52, 133, 159]. A successful, etiological/radical treatment in cancer would thus be mediated by the activation of an acidic pHi-mediated apoptotic chain reaction cascade ending in cancer cell death *(therapeutic apoptosis)* (Tables 1 and 3). Finally, preliminary trials in a clinical setting using different PPs and PTIs, either on their own or associated with chemotherapy, have been recently published in basic studies [141], animal models [160, 161] and humans patients with cancer [22, 133, 161-164]. However, some recent studies have shown a negative effect of the combination of certain chemotherapy protocols with proton pump inhibitors [27, 165].

pH dynamics and multiple drug resistance (MDR): an integral approach.

Historically, there have been different theories concerning MDR in cancer. The first one that was put forward stemmed from basic pharmacokinetics and the impact of protonation in drug uptake into the body from the acidified stomach. This theory states that low extracellular pH should oppose drug uptake since drug protonation impedes their transmembrane movement across the cellular bilayer membrane, especially if the drugs are weak bases**,** such as doxorubicin (pKa~8) [23, 56, 166]. While this can apply to weak bases, the pH gradient should not interfere with drugs that are weak acids or neutral. To understand the efflux of drugs in these cases, a P-glycoprotein (P-gp)-mediated resistance was then suggested. Initially, the P-gp approach to justify MDR seemed to fit with all the most important aspects of biochemistry. However, little attention had been paid until recently to the fact that drug-handling via P-gp also needs a pH gradient to function. So, the question as to whether and how the drugs come into contact with P-gp to be expelled has remained open for a long time. Furthermore**,** the ability of P-gp to handle, literally, almost hundreds of chemically different compounds challenges the notion of specificity (defined as very high affinity). Indeed, how a single glycoprotein can interact so efficiently with all those chemically different compounds is at least paradoxical.

To resolve this and other issues, a more integrated mechanism to explain MDR has been recently developed. This is based upon the modification of the dynamics of the tumor microenvironment through changes in the extracellular and intracellular pH [54, 55, 95, 167-174]. This model highlights the impact of the pH gradient in P-gp expression [175]. It has been demonstrated that the pH gradient stiffens cell membranes, constraining drugs to remain trapped within them for longer times, thereby increasing the probability of drug-P-gp interactions followed by extrusion [166, 172, 173, 176]. In this context the term “stiffening” refers to an imbalance between lipid interaction forces due to a pH change (Figure 2). From a parallel therapeutic perspective of pH-related resistance to therapy, the specific acid-base abnormalities of cancer metabolism significantly contribute to decrease, and even completely block, any immune reactivity against malignant tumors [177]. In all these cases, the therapeutic failure to induce cytoplasmic acidification and/or reverse PCR has been proposed to be the main underlying factor for MDR, because it also means resistance to the induction of the low pHi-mediated therapeutic apoptosis in either normal, slightly alkaline and/or highly alkaline cancer cells [18, 58, 150, 151]. The expression of P-gp leading to an elevation of pHi also correlates with a decreased plasma membrane potential in cancer cells, an electrical change that for a long time has also been regarded as a potent mitogenic and

carcinogenic stimulus [178]. This is apparently due to a pH-related P-gp overexpression and not to exposure to chemotherapeutic drugs [179, 180]. In line with this hypothesis, P-gp mediated resistance to imatinib in BCR-ABL-positive leukemia is reversed by NHE1 inhibitors like cariporide [181]. Similarly, intracellular acidification both decreases P-gp resistance in leukemia cells with high P-gp expression while also increases the cytosolic accumulation of drugs like doxorubicin [182]. Further, P-gp expressing cancer cells exhibit a significantly higher pHi than non-P-gp expressing cells**,** which to a certain degree accounts for the P-gp-mediated resistance [52]. Indeed, the fact that cells with an active P-gp transporter show a high degree of cytoplasmatic alkalinization has led some authors to conclude that P-gp can be mainly considered as a proton extrusion pump [159, 168, 171, 183]. Finally, intracellular acidification down-regulates P-gp**,** while extracellular acidification increases the activity of P-gp and induces MDR in rat prostate cancer cells and tissues [184] as well as in other tumors [185].

An integral interpretation of the Warburg effect for a selective antimetabolic approach to cancer therapy.

Another unique hallmark of cancer cells is their shift to glycolytic metabolism over oxidative phosphorylation (OxPhos), even under aerobic conditions. This was first described by Otto Warburg [186] and it is known as the Warburg Effect [100, 101].
During the last decade, the number of publications that explain the Warburg effect and how it functions have increased dramatically. However, apart from considering its early role in oncogenesis, a full explanation of the dynamics of its development in cancer cells and how it leads to cancer is still unresolved [187]. Early experiments of controlled oncogene activation showed that the first appearance of glycolytic metabolism occurs very early in the oncogene-driven transformation of normal cells and that its development was dependent on the initial oncogene-dependent cytoplasmic alkalinization [188, 189]. Indeed, as both the processes of OxPhos and gycolysis are exquisitely but oppositely pH sensitive, a rapid shift of cell metabolic patterns follows alkalinization. No matter that these concepts belong to the new pH-centric paradigm, a discussion of the effects of acid-base changes on glycolysis and the dependence of the metabolic balance between glycolysis and oxidative phosphorylation on pH was already described more than four decades ago. However, at that time there was the exclusive emphasis on a physiological and not on an oncological perspective [190].
Besides, there is increasing evidence that both pHi and pHe are important in driving this ever increasing dependence on glycolysis and decreasing dependence on OxPhos as the tumor progresses [134, 191]. Indeed, as both the processes of OxPhos and gycolysis are exquisitely but oppositely pH sensitive, a rapid shift of cell metabolic patterns follows alkalinization. Besides, a great deal of evidence supports the fact that it is the alkaline pHi present in cancer cells which is the primordial driver of this metabolic shift, and that this change is one of the ‘corner-stones’ in the altered metabolism underlying neoplastic transformation and progression and such reciprocal metabolic shift may well be one of the most sensitive pHi sensors of a cell. This adds further weight to the current opinion that among the uncountable allosteric factors that regulate the glycolytic sequence, the intracellular pH (pHi) is by far the most decisive one [71]. Indeed, recent publications also lead to the conclusion that the Warburg Effect may be completely explained through the elevation of pHi in cancer cells [31, 57, 71, 192].
Lower extracellular pH (pHe) (in both the presence and absence of extracellular lactate) also shows profound effects on tumor cell gene expression, including genes involved in

glycolysis [103]. Furthermore, the inhibition of NHE1 results in changes in the expression patterns of a number of genes including many that regulate cellular metabolism [193]. Recently, the relationships between pH and every step of the glycolytic chain, as well as the metabolic changes relating pH, glycolysis and the pentose phosphate pathway and their respective roles in tumor metastasis have been thoroughly reviewed [71, 194]. Therefore, these complex dynamics of the role of pH in intermediary metabolism starts with the first oncogene-driven pHi change and it is this very early alteration of pH dynamics and the consequent metabolic disruption, which sets the stage for the conditions necessary for tumor growth and metastatic progression, further illustrating the pH-centric paradigm for carcinogenesis and metastasis.
Interestingly, neoplastic progression is considered to be the result of a clonal selection of increasingly more aggressive cells. However, the accumulation of genetic defects resulting in malignant cells is faster than theoretically predicted. Recently, this contradiction has been solved with the observation that the tumor microenvironment drives the selection of aggressive cells within a tumor by contributing to tumor genetic instability [104-106]. Thus, cancer is a prototype of the paradigm of a positive feedback of genotype and phenotype interactions in which the resulting phenotype from the initial genotypic alteration promotes further genotypic alterations in a self-fed vicious and thermodynamically-wise advantage cycle [43]. This fundamental role of pH regulation (driven by NHE1 and other proton transporters) in modulating cellular metabolism is perhaps not surprising considering the postulated role of an ancient NHE together with ATP synthase in the origin and development of chemiosmotic coupling and bioenergetics [195]. Indeed, the proper functioning of mitochondrial OxPhos metabolism is dependent on a high, constant and finely regulated cytosol-mitochondrial proton gradient [43, 196, 197].

pH and the Warburg effect in therapeutics.

From the therapeutic point of view, inhibiting tumor glycolysis [198] and reversing the Warburg effect by selective intracellular acidification has already been considered as a treatment in cancer therapeutics [31, 95]. Indeed, in the light of both older and more recent contributions [19, 31, 199, 200] it can be concluded that counteracting the Warburg effect and aerobic glycolysis to selectively induce intracellular acidification and/or reverting PGR in cancer cells now appears to represent the same phenomenon [9, 31, 57]. This advances a rational and firmly based approach to cancer treatment of all malignant tumors. In summary, the most potent and promising amiloride and non-amiloride derivatives, such as Cariporide, Phx-3 and compound 9t [57, 71, 142] need to be urgently included in pre-clinical and clinical trials as an important part of the anticancer armamentarium, either alone as single anticancer drugs and/or associated to other synergistic methods and therapies, such as antiangiogenics [137, 138]. In addition, the most potent NHE1 inhibitors, as well as other PTI inhibitors, should be considered as chemotherapeutic agents on their own, since they are able to induce intracellular acidification and/or reverse the abnormal PGR of cancer cells and tissues. It can be advanced that they show a great promise as a new and selective approach to the treatment of a wide array of different malignant tumors, even leukemias, and their use in bedside oncology should help to overcome the present impasse and flat progress in cancer treatment [201].

Non-proton transport intracellular acidifiers with strong anticancer properties.

There is a large family of cellular acidifiers not directly related to PTI that have shown strong anticancer properties and, here, are considered as a group for the first time.

Salinomycin

Salinomycin is a K^+ ionophore antibiotic isolated from *Streptomyces albus* known to have a strong anti-cancer activity. Salinomycin kills cancer stem cells in different types of human cancers by interfering with ABC drug transporters, the Wnt/β-catenin signaling pathway, mitochondrial function and other CSC pathways [202, 203]. By comparing the chemical structures and cellular effects of this drug with those of valinomycin (K^+ ionophore) and nigericin (K^+/H^+ exchanger), these authors concluded that salinomycin mediates K^+/H^+ exchange across the inner mitochondrial membrane. Clinically, this drug has been able to induce partial regressions of heavily pretreated and therapy-resistant cancer patients [204]. The antitumor mechanisms described for salinomycin activity include the efflux of intracellular K^+ and a reduction of pHi, an increase in intracellular Ca^{2+} and a down-regulation of MDR. Such antitumor mechanisms are connected to its strong affinity especially to potassium cations. Salinomycin promotes the outflow of K^+ from the mitochondria as well as cytoplasm, and similar to other ionophores mediates in a H^+ /K^+ exchange across lipid membranes. This in turn leads to an increase in intracellular Ca^{2+} and a down-regulation of MDR [205]. However, the inhibition of mitochondrial Na^+/Ca^{2+}-exchangers (NCX) by CGP-37157 was shown to inhibit the mitochondrial Ca^{2+} accumulation induced by Salinomycin, while maintaining its antineoplastic efficacy [206]. While this approach indicates a route to reduce or prevent salinomycin-induced neuropathy, it also rules out a main potential anti-cancer mechanism, i.e. mitochondrial Ca^{2+} accumulation. The antineoplastic effect of this and other ionophores is believed to be mainly due to their ability to directly acidify the intracellular environment since DNA synthesis stops as cell pHi decreases [207], confirming a direct relationship between pH and DNA synthesis, a feature that has been known for decades [208]. Finally, it has been recently shown that the cytotoxic effect and authopagy inhibition associated with Salinomycin was dramatically enhanced in acidic conditions, cellular acidification that increases autophagic elimination of mitochondria (mitophagy), a feature that has also been proposed to underlie the pathogenesis of several neurodegenerative diseases [209, 210]. Therefore, acidity iarond tumors may represent the fuel supporting the transfer of cations across biological membranes via K^+/H^+ exchange.

Valinomycin

Valinomycin, another K^+ ionophore, triggers a rapid loss of mitochondrial membrane potential and precedes cytoplasmatic acidification in murine pre-B cell lines, which leads to cysteine-active-site protease activation, DNA fragmentation and cell death [211].

Niclosamide

Niclosamide belongs to the anthelmintic family especially effective against cestodes that infect humans. Niclosamide has been shown to exert antiproliferative activity in a broad spectrum of cancers, including acute myeloid leukaemia cells and solid tumors, like colon cancer, breast cancer and prostate cancer [212, 213]. Besides the fact that niclosamide is known to hit many different intracellular signaling pathways (e.g. β-

catenin, Notch, and mTORC1 pathways) [212], experiments in both breast cancer cells and cell-free systems demonstrated that this drug possesses cellular protonophoric activity by pumping protons from lysosomes to the cytosol down their concentration gradient, therefore leading to an effective lowering of cytoplasmic pH [214].

Disulfiram

The thiocarbamate alcoholism drug disulfiram, normally used to block the processing of alcohol in the body, has been shown to block the P-gp extrusion pump and to inhibit the transcription factor nuclear factor-kappaB (NFKB). In this way, it sensitizes tumors to chemotherapy, reducing angiogenesis and inhibiting tumor growth *in vitro* [215]. Disulfiram has also been shown to inhibit human melanoma growth *in vitro*, both in mice and in a patient with metastatic disease. This study also reported that, at currently approved doses for alcoholism, the combination of oral zinc gluconate and disulfiram also induced a >50% reduction in hepatic metastases and produced a long term clinical remission in a patient with stage IV metastatic ocular melanoma. While the relationship of pHi to Disulfiram is not known, an acidic tumor microenvironment enhances the cytotoxicity of disulfiram/Cu^{2+}Antabuse complexes in MCF-7 breast carcinoma and HT-29 colon carcinoma cells [216].

Lovastatin

It has been previously shown that statins exhibits antiproliferative activity against cancer cells, representing a category of drugs available for clinical use. Recent trials show that the addition of statins to traditional chemotherapeutic protocols increases the efficacy of chemotherapy in statin-sensitive tumors [217]. It has also been demonstrated that Lovastatin (LOV)-induced apoptosis is associated with dose-dependent intracellular acidification, and this correlates with the extent of DNA degradation. Importantly, this activity was suppressed by NHE1-driven intracellular alkalinization [218]. These observations provide a further connection between the activation of the NHE1 and the suppression of apoptosis seen in resistance to chemotherapy [144]. Finally, LOV, as other statins like atorvastatin and simvastatin, is known to be a MCT1 inhibitor [219].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Some NSAIDs, such as Diclofenac, Diflunisal and Aspirin are also known for having anti-cancer effects. Lactate is transported out of the cancer cell by monocarboxylate transporters (MCTs) [36] and NSAIDs with monocarboxylic acid structures, such as Diclofenac, have been reported to inhibit MCTs [220]. Since Diclofenac blocks tumor cell proliferation via MYC and ciclo-oxigenase (COX)-dependent and independent mechanisms, it was concluded that Diclofenac holds a potential as a clinically applicable MYC and glycolysis inhibitor to be utilized together with established tumor therapies [220]. In this regard, a significant intracellular accumulation of lactate in cells treated with Diclofenac preceded the observed effects on gene expression, suggesting a direct inhibitory effect of Diclofenac on lactate efflux, probably through a lowering of pHi. These results further show that lactate efflux, PGR, pH, glycolysis and tumor growth are closely related as belonging to the same integral, hierarchically organized and selective metabolic strategy of cancer [18, 69, 221].

Metformin

There is growing evidence for a role of metformin in tumor chemotherapy [222], for instance in breast cancer [223, 224]. Metformin should be suggested as a supporting

element for treatment with PTIs because it acts through on mitochondrial respiration by inhibiting the complex I of the electron transport chain, hence blocking oxidative respiration. As a result of this effect, the dependence of cancer cells on glycolysis is increased, and it can additionally be targeted with PTIs. Also, metformin may potentiate the therapeutic strategy of disrupting the export of lactate by blocking MCT1 function. Consequently this leads to an accumulation of intracellular lactate and a decrease in pHi that rapidly disables tumor cell growth and glycolysis [225, 226]. Furthermore, metformin is also effective in inhibiting colony formation and proliferation by targeting acidic melanoma cell populations, this disclosing a potential addition to the treatment of advanced melanoma therapy [227]. Finally, another biguanide, like phenformin, has also been ascribed to have an anticancer effect via mechanisms involving disruption of MCTs [221].

Perillyl Alcohol (POH).

The monoterpene perillyl alcohol (POH) is isolated from the essential oils of several plants. It shows anti-cancer effects presumably related to its Na^+/K^+-ATPase inhibitory properties as well as to its activity as an intracellular acidifier, similar to cardiac glycosides [228, 229]. POH has been used in the treatment of several malignant tumors, including gliomas [230]. It also induces growth arrest and apoptosis of leukemia cells [231]. There are occasional but impressive reports of complete remissions of recurrent glioblastoma treated with POH via intranasal administration [232]. Also, POH administrated via inhalation, concomitantly with oral temozolomide, has been reported to halt the progression of recurrent glioblastoma [233].

3-Bromopyruvate (3BP)

A certain success in treating advanced cancers with 3BP has already been demonstrated in the clinical setting [234, 235]. Multiple reports indicate that the small molecule "energy blocker" 3BP transport into cancer cells is mediated by H^+-coupled or Na^+-coupled MCTs. MCT1, in particular, is essential to its cytotoxic action [234, 236]. Indeed, these studies on the mechanism by which 3BP enters cancer cells suggest that the pH gradient from the extracellular environment to the cell cytoplasm may be crucial since the tumoral extracellular acidic pH increases the affinity for 3BP uptake, an effect possibly due to the up-regulation of MCTs. As a result, this will enhance its selective cytotoxic effect in tumor cells [234, 236]. This typical acid-base abnormality of the malignant tumor microenvironment could also explain the lack of secondary effects of 3BP already described in *in vivo* studies. In addition, it has also been shown that 3-BP inhibits glycolysis and mitochondrial respiration inducing cell death in leukemia cells while also acting as a chemosensitizing agent [237].

Dichloroacetate (DCA)

Dichloroacetate-treated tumor cells show inhibited expression of two key pH regulators: MCT1 and V-ATPase, apart from altering the expression of GLUT1 and HIF-1. DCA shows a tumoricidal effect on murine T cell lymphoma cells by triggering apoptosis, showing that DCA-dependent alteration of tumor cell survival involves pH homeostasis and glucose metabolism [238]. Different case reports of human malignancies reversed by DCA have been published [239].

Nigericin

Many other cellular acidifying agents have been studied as anticancer agents for at least the last three decades. Among these compounds were: stilbene disulfonates (Cl^-/HCO_3^-

exchanger inhibitors), nigericin, DIDS, or the protonophore carbonylcyanide-3-chlorophenylhydrazone (CCCP). Along with amiloride and some of its analogs, nigericin was one of the first intracellular acidifiers studied by the group of Tannock in a series of seminal publications in the field [240-245]. These authors also showed an increased anti-tumoral effect of amiloride when combined with nigericin [240]. More potent amiloride derivatives, such as 5-(N,N-hexamethylen) amiloride (HMA) and ethylisopropyl amiloride (EIPA), together with nigericin, were also reported to consistently inhibit tumor growth [242]. Finally, the cell acidifying role of nigericin can be explained because nigericin is a ionophore that exchanges K^+ for H^+ across most biologic membranes in a similar way than Salinomycin does [246].

Hyperthermia and radiation and the NHE1-pHi relationship.

There has recently been a renewed interest in treating tumors with hyperthermia. Hyperthermia has been reported to decrease pHi [247]. A number of studies show that lowering pHi (almost all by targeting NHE1) can strongly enhance the thermosensitivity of cancer cells [248-252]. Therefore, there are very real possibilities for the combined use of PTIs together with hyperthermia [253]. Furthermore, the combination of hyperthermia and radiation has also been exploited in cancer treatment [254]. Other relationships between pH, radiation and hyperthermia have been reviewed elsewhere [255].

Docosahexaenoic acid (DHA) and polyunsaturated Omega-3 long-chain fatty acids

The polyunsaturated n-3 fatty acid DHA (docosahexaenoic acid, 22:6n-3) is effective in increasing survival and chemotherapy efficacy in breast cancer patient with metastasis [256], in controlling cancer cell growth [257], in inhibiting the growth of malignant cells [258] and inhibiting survival pathways in cancer cells [259]. The ion channel NaV1.5 has been shown to promote MDA-MB-231 breast cancer cells invasiveness by potentiating the activity of NHE1 [260, 261] . DHA inhibits NaV1.5 current and NHE1 activity in human breast cancer cells, and in turn reduces NaV1.5-dependent cancer cell invasiveness [262]. Similarly, the use of nutritional lipids in the diet, like omega-3 long-chain polyunsaturated fatty acids has been suggested to reduce the invasion of breast cancer cells and to block the development of metastases [263]. This kind of dietary interventions might represent further therapeutic opportunities in association with conventional anti-cancer treatment.

Cardiac glycosides

By inhibiting Na^+ /K^+-ATPase, cardiac glycosides have been shown to secondarily inhibit NHE1, induce intracellular acidification and, thereby, stimulate apoptosis in cancer therapy [229]. Digoxin and digitoxin have been shown to be anticancer agents at doses used in human cardiological settings [228, 264-267]. Other cardiac glycosides that have shown anti-cancer properties are bufalin, oleandrin and ouabain. Finally, agents like phenytoin, carbamazepine, valproate, lamotrigine, ranolazine, ropivacaine, lidocaine, mexiletine, flunarizine and riluzole have been recently reviewed and therapeutically repurposed because of their capacity to act as antimetastatic agents after targeting voltage-sodium channels [268].

Urocanic acid

When an effective amount of urocanic acid is administered, this drug is able to acidify the cytosol causing inhibition of proliferation of both transformed and non-transformed

cells. The use of urocanic acid as an enhancer of other therapeutically active agents has also been disclosed [269].

Photodynamic acidification

Using a photosensitizing agent the pHi of MDA-MB-231 triple negative breast cancer cells (TNBC) drops leading to apoptosis, suppressing tumor growth and increasing survival in mice [270].

Ion channels in cancer and neurodegeneration.

Some ion channels are significantly involved in both the regulation of pHi/pHe in cancer cells and in the acquisition of proliferative and pro-invasive capacities. Ion channels regulate several cell processes, such as cell proliferation, resistance to apoptosis, cell adhesion, cancer cell motility and extracellular matrix invasion. They also participate in tumor progression through non-excitable functions [271-278]. Consequently, an altered physiology of ion channels has also been proposed as a new hallmark of cancer cells and as a potential target for selective therapeutics [273-281]. On the contrary, cellular acidification resulting from brain ischemia, either preceding or accompanying the clinical manifestations of certain HNDDs in the central nervous system (CNS), has been shown to be dramatically deleterious in provoking neurodegeneration through the participation of pH-sensitive or pH-regulating ion channels [35, 37, 271, 272] **(Figure 3).**

A) Relationships between deregulated tumor pHi/pHe and voltage-gated ion channels in cancer.

The homeostasis and allostasis of the pHi/pHe gradient also participates in the control of cellular resting membrane potential (Em) [282]. This is critical in excitable cells, such as in neurons, for triggering and propagating action potentials This is critical in excitable cells, since it both triggers and propagates action potentials. In non-excitable cells, membrane hyperpolarization is associated with normal stem cell differentiation and inhibition of mitosis [178]. On the contrary, a depolarized Em has been identified as an important parameter favoring cancer cell proliferation and migration, and proposed to be essential to maintain cancer stem cells abilities. In this regard, there are several ion channels that are directly gated or their activity modulated by extracellular H^+ including the Acid-sensing Ion Channels (ASIC) [283], the sensory and pain receptor Transient Receptor Potential Vanilloid receptor 1 (TRPV1) [284, 285], the Transient Receptor Potential Ankyrin repeat receptor 1 (TRPA1) [286, 287]**,** some two-pore domain (K2P) [288], inwardly rectifying K^+ channels (Kir) [289] and the voltage-gated Na^+, Ca^{2+} and K^+ channels [290]. As a result, a deregulated pH homeostasis will also have dramatic results in either hypo- or hyper-excitability in excitable cells [271] and will also affect cell volume, secretion and proliferation, properties which are also under the dependence of ion channel activity in non-excitable cells, such as in epithelial cells [291].

On the other side, there is a group of voltage-gated H^+ channels (Hv) and their activation results in an outward current, extruding the excess of intracellular H^+ and, therefore, participating in the acidification of the extracellular compartment while affecting membrane potential [292]. Some studies have identified Hv as being involved in cancer progression. In highly invasive breast cancer cells from the MDA-MB-231 cell line, Hv1 was found to be highly expressed, while it was not, or it does it very weakly, expressed in poorly invasive MCF-7 cells. The down-regulation of Hv1 reduces

breast cancer cell migration and invasion in highly metastatic cells and is responsible for inducing intracellular acidification, which indicates a role of Hv1 in the regulation of resting pHi [293]. In another study, the same authors showed that Hv1expression was significantly correlated with tumor size and clinical stage [294]. Furthermore, the high expression of Hv1 in biopsies was associated with poor prognosis and a shorter recurrence-free and overall survival. *In vitro,* knockdown of Hv1 expression in invasive MDA-MB-231 cells decreases cell proliferation, invasiveness and tumor growth, inhibiting proton secretion, acidification of the extracellular microenvironment and ECM degradation. Hv1 was also found to be strongly expressed in colorectal adenocarcinomas, but not or lowly expressed in normal tissues or in hyperplastic polyps [295]. Also in this kind of tumor, the levels of Hv1 expression correlate with tumor size, lymph node status and clinical stage [295]. Besides, high Hv1 expression is significantly associated with shorter overall and recurrence-free survival, and the inhibition of Hv1 activity in colorectal cancer decreases cell invasion and migration by blocking proton extrusion and intracellular pH recovery [295]. Finally, different inhibitors of the Hv1 voltage-gated proton channels are now being studied as anticancer agents [296].

B) Relationships between pH, NHE1 and the voltage-gated sodium channels in cancer.

Voltage-gated sodium channels (Na_V), carrying inward charges upon gating, are known to be responsible for membrane depolarization and critical for "excitable" cells such as neurons, skeletal and cardiac muscle cells, as well as for the initiation and propagation of action potentials [297, 298]. They were initially identified as being characteristic of excitable cells. However, they are also found to be unexpectedly expressed in cancer cells, especially in those of epithelial origins (prostate, breast, lung, colon, cervix and ovary), while they are not expressed in the same non-cancer tissues. This has led to consider them among the new hallmarks of cancer [281]. Their function is associated with cancer progression [277, 299, 300], metastases and patient death [301, 302] (Figure 3). In highly aggressive human breast cancer cells, the activity of the $Na_V1.5$ isoform was not associated with the triggering of action potentials but it enhanced extracellular matrix (ECM) degradation and cancer cell invasiveness by increasing the activity of the extracellular cysteine cathepsins B and S [300, 303] which have maximal activity in acidic conditions [304]. While the mechanistic details by which Na_V promote**s** cancer cell invasiveness are not fully characterized, it has been demonstrated that invasiveness of malignant cells takes place by persistent $Na_V1.5$ activity (through a persistent window current at the membrane potential). This occurs through the interaction of $Na_V1.5$ with NHE1, which by extruding H^+ and so acidifying the pericellular microenvironment then activates cathepsins [260, 303]. Indeed, $Na_V1.5$ activity is responsible for the allosteric modulation of the NHE1, rendering it more active at pHi values between 6.4 and 7. It was suggested that the sodium current was responsible for this regulation[260, 261]. Furthermore, NHE1 and $Na_V1.5$ proteins can be co-immunoprecipitated and may physically interact in invadopodia [260, 261]. In summary, the activity of Na_V channels in cancer cells has been identified as an important parameter favoring cancer migration through a persistent sodium current that would tend to depolarize the membrane potential of malignant cells [305] while favoring the reversed proton gradient in cancer cells.

From a therapeutic point of view, the use of Na_V-inhibiting drugs has been proposed in order to reduce cancer progression, so increaseing survival time in patients with cancer [268, 277, 306, 307]. Indeed, inhibitors of Na_V that are clinically used for the treatment of other pathologies, such as ranolazine for the treatment of chronic angina or phenytoin

as an anticonvulsant, are powerful pharmacological tools that have been shown to prevent metastatic colonization of organs of immunodepressed mice [308, 309]. These studies indicate that inhibitors of Na_V channels, already approved for other clinical uses such as antiarrhythmics, anticonvulsants [302, 310] and anaesthetics [311], as well as other compounds [268], can be repurposed for antiinvasive cancer treatment and even for the prevention of metastatic development.

C) Ca^{2+} homeostasis and NHE1.

In glioma cells there is a persistent NHE1 activity consistent with depolarized membrane potentials, calcium loading, high intracellular pH and Na^+ levels. Importantly, while inhibition of NHE1 by cariporide is not toxic to glioma on its own, its combination with the inhibition of the Na^+/Ca^{2+} exchanger NCX1.1 selectively kills these brain tumor cells [140]. This is consistent with the growing evidence that Ca^{2+} homeostasis is importantly remodeled through the participation of multiple Ca^{2+} channels and transporters. These are expressed at the plasma membrane or in intracellular compartments, participating in enhanced proliferation, cancer cell survival and invasion [279]. A graphic representation of ion channels and their effects on cancer and neural cells is shown in Figure 3. Changes in intracellular Ca^{2+} concentration, would, in turn, modulate the activity of NHE1, known to be Ca^{2+}-sensitive through the binding of calmodulin to a specific domain of NHE1 [312, 313]. Therefore, the activity of numerous Ca^{2+}-permeant ion channels that are deregulated in cancer might also participate in the regulation/deregulation of pHi/pHe and associated cellular functions.

D) Relationships between pH and ion channels in neurodegeneration.

The central nervous system (CNS) demands a tight control of acid-base homeostatis within very narrow limits in order to properly maintain neuronal excitability, synaptic transmission and neurotransmitter uptake [37, 271, 272, 314]. Changes in pHe, mostly resulting from metabolic stress are deleterious to the CNS and can result in several HNDDs [37, 271, 272, 314]. Indeed, ischemic brain injuries that induce toxic intracellular Ca^{2+} overload produce a deviation towards cellular acidification followed by downstream activation of proteolytic cascades in neurons [315, 316] (Figure 3). This Ca^{2+} overload was initially proposed to be mediated by the excessive release of the neurotransmitter glutamate leading to the over-activation of glutamatergic excitatory NMDA receptors [310, 317].

Furthermore, activation of acid-sensing Ca^{2+}- permable channels expressed during acidosis in peripheral and CNS neurons also modulates network electrical activity and exacerbates neuro-degeneration in mice [318]. Spontaneous neurotransmitter release was reduced by ASIC1a activation at motor nerve terminals and these effects were emulated by acid solutions [319]. In this respect, it has been hypothesized that the intracellular H^+ concentration, acting as a second messenger or via modulation of ion channel activity governs neuronal excitability [320]. This lowering of CNS pHi stimulates the opening of ASIC1 channels and a cellular entry of $Ca^{2+,}$ which further damages many cellular functions and even provokes neural cell death (Figure 3) [321]. In amyotrophic lateral sclerosis (ALS), intracellular acidification-mediated apoptosis is involved in the Ca^{2+}-dependent glutamate mediated neural cell death that is considered to be responsible for disease progression [321, 322].

The hypoxic tumoral microenvironment is quite similar to what happens during brain ischemic hypoxia or strokes and, apparently, also in certain HNDDs (Figure 3). In these situations, oxygen depletion forces brain cells to use anaerobic glycolysis for the production of ATP, which induces the accumulation of lactic acid and H^+ in the extracellular compartment and causes pHe acidification to values between 6.0 and 6.5 [323]. These low pHe conditions further aggravate ischemic brain damage, neuronal injury and glial cell death [296, 324, 325]. Importantly, cell death induced by acidosis was inhibited by ASIC blockers and cells lacking endogenous ASICs were resistant to acid injury [272]. This pHe-driven and ASIC-dependent mechanism was further demonstrated *in vivo* in focal ischemia, for which the intracerebroventricular injection of ASIC1a blockers, or knocking-out the expression of the ASIC1a gene, protected the brain from ischemic injuries [326]. Multiple studies have supported the participation of homomeric ASIC1a channels, as well as of heteromeric channels composed of ASIC1a and ASIC2b [327] in acid-mediated neurotoxicity. Recently, it was demonstrated in CA1 hippocampal neurons, which are highly vulnerable to ischemic stroke, that ASIC1a activation under extracellular acidosis contributes to post-ischemic glutamatergic Ca^{2+}-permeable AMPA receptor plasticity. This identifies a functional interaction between acidotoxicity and excitotoxicity and suggests that ASIC1a and Ca^{2+}-permeable AMPA receptors are potential drug targets for neuroprotection [328]. In addition to ischemic stroke, ASICs have now been implicated in many other pathologies in the CNS, such as multiple sclerosis, Huntington's disease, Parkinson's disease and spinal cord injury (for a review, see ref [329]). Thus, the pharmacological targeting of ion channels such as ASICs [261, 276, 326], glutamatergic Ca^{2+}-permeable receptors and/ or even Na_V channels [307] could represent new strategies for the treatment of either malignant disease and in the prevention and treatment of post-ischemic and neurodegenerative pathologies. In summary, there is an increasing amount of evidence that pH-linked ion channels pathophysiology present a potential therapeutic effect both in human cancer and in improving understanding of HNDDs pathogenetic mechanisms as well as leading the way towards novel and cutting-edge forms of treatment in both situations.

Cell death and neuroprotection in HNDDs. A transversal extension from the pH-centric translational cancer paradigm to the etiopathogenesis and therapeutics of neurodegeneration.

The pH-centric cancer paradigm in HNDDs.
Is the intracellular pH a key homeostatic factor for understanding and treating human neurodegenerative diseases?

The pH-centric paradigm can be applied to HNDDs in order to improve our understanding of the nature of the abnormalities underlying the pathological deregulation of neural cell death and/or malfunctioning [330-334]). In this context, a pH-related approach helps to clarify many of these two metabolically and biochemically opposed situations: cancer and neurodegeneration. This new approach is based upon the fact that, regarding cellular acid-base homeostasis, cancer and HNDDs, such as Alzheimer's disease (AD) and other HNDDs can be looked at as two situations at both opposite ends of the metabolic spectrum (Table 1) [35-39, 331, 334, 335]. This perspective also leads to a new integral paradigm pointing towards a unified theory of the apoptosis-antiapoptosis machinery and/or the cellular programmed pro-death/anti-death mechanisms. It will also help to understand the scientific reason behind the fact that in epidemiological studies AD and cancer show an inverse association among them [336].

In order to better understand these dynamics it is necessary to take into account the effects of acid-base disturbances on neuronal functions and what is known about the role of acid-base regulatory mechanisms in blocking the lowering of neuronal pHi under physiopathological conditions, a subject that has been increasingly considered over the years [37, 38, 271, 272, 314, 330, 333, 335, 337-340]. Intracellular acidification has been found to be more pronounced in the brains of AD patients [272, 335] and ß-amyloid aggregation in AD is induced by acidosis and is reverted upon microenvironmental alkalinization [341]. Most importantly, while acidification provokes neural cell death, pHi alkalinization shows beneficial effects on the evolution of ALS in mice [307, 321, 335, 341]. Seminal work in this area [39] showed that lowering pHi of neurons from 7.36 to 7.09/7.00 through exposure to nitric oxide (NO) sets in motion a programmed cell death program, increasing DNA fragmentation and decreasing neuronal survival ("low pHi-mediated metabolic collapse"). Indeed, intracellular acidification determines apoptosis and other related cell death programs and mechanisms [36, 37, 271, 342, 343]. In neuronal injury this apoptotic phenomenon is induced by the activation of three low pHi-dependent endonucleases [39, 344].) Thus, the importance of maintaining a strict and narrow range of pHi/pHe homeostasis in the CNS neural cell protection becomes evident since it controls neuronal hyper- and hypo-excitability, synaptic transmission, neurotransmitter uptake, intercellular communication, nociception and inflammation. Indeed, the cellular death that spontaneously takes place in HNDDs like AD [345] seems to represent the same phenomenon that occurs in cancer therapeutics designed to selectively induce pro-apoptotic acidification that aim to lower pHi below survival levels through a wide array of different approaches and methods as discussed above (Tables 1 and 3).

Recent studies in an *in vitro* model of excitotoxic neuronal death reported that the potent NHE1 inhibitor cariporide, perhaps paradoxically at first sight, protected neurons from ischemic injury and this effect was ascribed to the prevention of CNS apoptosis. In that study, cariporide (100 nM) was found to reduce both glutamate-induced necrotic and apoptotic neuronal cell death. Cariporide attenuated glutamate-mediated mitochondrial death pathways involving loss of mitochondrial membrane potential as well as Ca^{2+} and reactive oxygen species (ROS) accumulation [346]. These results further suggest that, at least indirectly, NHE1 participates in the necrotic cell death process and that its inhibition offers a means of preventing both necrosis and apoptosis. In the same vein, PPIs seem to increase the risk of dementia, probably through a pH effect [347].

Also the more general NHE inhibitor, amiloride, has been shown to have protective effects in different neurodegenerative situations by preventing acidosis-induced cation overload and preserving myelin levels in hypoxic and inflammatory conditions [348]. These results further suggest that, at least indirectly, NHE1 participates in the necrotic cell death process and that its inhibition offers a means of preventing both necrosis and apoptosis. Among the different proton transporters, NHE1 appears to be the main mechanism that drives neural cells to a pathological decrease in pHi and, therefore, towards cellular death through cytosolic acidification [37, 349]. That is, blocking NHE1 activation with cariporide may provide neuroprotection following brain hypoxia by protecting cells from Ca^{2+} entry and ROS [350]. Interestingly, it has also been shown that patients' Interestingly, it has also been shown that the patients' lymphoblasts mirror that which takes place in the nervous tissue in terms of NHE1 activity and pH regulation, suggesting that this might serve as a potential non-invasive test of the response of neural disease to different therapies [314]. Namely, treatments that best

return lymphoblast pH towards physiological values should do the same to the nervous tissue [314].
Finally, while the genetic conditioning and background of the pH/NHE system has been considered in the field of oncology [33, 193], we are not aware that these relationships have been ever considered in HNDDs in spite of multiple studies following different research lines in the study of the genetics of HNDDs [351-353].

Growth factors and melatonin in HNDDs and cancer. Lack of trophic factors leads to decreased trophism and mobility.

A) Deficiencies of human Growth Factors (hGFs) and other hormone deficiencies in HNDDs.

In many cell types, including those of the hematopoietic system, removal of essential growth factors results in apoptosis [354]. The general concept behind this perspective is very simple: HNDDs have been shown to lack of different trophic and/or growth factors, and a general characteristic of HNDDs is "lack of trophism and/or mobility [35]. Thus, the most rational therapeutic approach would be to provide the missing trophic factors and/or to stimulate the deficient systems involved. Perhaps, a certain unawareness of this feature is behind the overall failure in the treatment of HNDDs and many other degenerative processes, from joint degeneration in chronic arthritis to peripheral nerves neurodegeneration [36, 37, 355]. The problem is to know why and how the lack of certain hGFs leading to neurodegeneration appears, and whether a decrease of neural and/or non-neural hGFs factors is directly responsible for the different neurodegenerative processes. In this line, there is evidence from animal and human studies that link cognitive deficits with changes in brain and peripheral trophic factors, while exercise, by increasing the levels of IGF-1 and other neural and non-neural in origin growth factors, induce cognitive improvements in different HNNDs [356].
An important aspect of this concept is that pH regulation and NHE1 activity is known to be a fundamental mechanism in the pHi regulation in the CNS [349]. It has also been known for a long time that different growth factors, platelet-derived (PDGF) or otherwise, activate NHE [123, 357]. This increases intracellular pHi and stimulates cellular metabolism and DNA synthesis [358]. From these pathogenetic associations a direct therapeutic consequence is easy to recognize now [98, 123, 359] possibly leading to the right approach to the treatment of at least some HNDDs (Figure 1) [35, 36].

B) Human growth hormone (hGH) in HNDDs and melatonin (MT) in HNDDs and cancer. A beneficial side-effect of the new therapeutic trends?

I -hGH in HNDDs

Ageing is related to the progressive lack of a number of neurotrophic factors, including human growth hormone (hGH) among them, this decay being considered a physiological process [360]. For decades, hGH administration in elderly people has been reported to improve cognition and metabolic alterations typical of old age [361]. The effects of hGH on cognition have been widely documented, particularly on learning and memory [362, 363]. Moreover, a recent study in injured rats demonstrated that hGH treatment had a positive effect on cognitive function, most likely by increasing expression of hippocampal and prefrontal Brain Derived Nerve Factor (BDNF) and

Tyrosinkinase B (TrkB) [364]. hGH and its receptor (GHR) are produced in neural stem cells in all animal species studied and this local production leads neural stem cells to proliferate, differentiate, migrate and survive. For these effects Pi3K/Akt and ERK 1/2 play a key role [321]. In rats, growth hormone (GH) administration cooperates with locally-produced GH (non human growth hormone) in brain repair after an injury and peripheral GH induces neural cell proliferation in the intact adult rat brain. However, the last upstream factor responsible for cellular survival is the activation of jun n-terminal kinase (JNK) [365]. Indeed, exogenous hGH administration cooperates with locally-produced hormone in increasing the proliferative response of hippocampal progenitors to an injury [366]. Moreover, hGH may facilitate brain plasticity and early hGH treatment promotes relevant motor functional improvement after severe frontal cortex lesions in adult rats [367].

Importantly, hGH also induces the expression of a number of neurotrophic factors (IGF-I, EGF and its receptor, EPO, VEGF, NGF) (Figure 1) and increases the cerebral metabolic turnover of NA (Noradrenaline) and DA (Dopamine) [360, 367-372]. While wit is known that neural progenitors are produced at the cerebral level in different neurogenic niches along the whole life, their production also progressively decreases as the subject ages. It remains to be established whether the effect of hGH administration might compensate this physiological age-related decrease production and/output of different human growth factors (HGF), neural-derived or otherwise, but preliminary results from our group indicate that this occurs [373]**.** While the neurotrophic effect of hGH, either exerted by itself or by inducing the expression of a number of neurotrophic factors is now clear (Figure 1), no long ago it seemed that this effect was exerted only after a traumatic brain injury (TBI) or after a stroke or in children with cerebral palsy, when suffering GH-deficiency as a result of the brain insult. However, the positive effects played by GH on brain repair after an injury have been also demonstrated in TBI patients without GH-deficiency [374, 375]. In spite that hGH concentrations are low in the cerebrospinal fluid of patients with Amyotrophic Lateral Sclerosis (ALS), a clinical trial demonstrated that hGH administration exerted no effect in the clinical progression of this fatal neurodegenerative disease [375, 376]. However, studies *in vitro* and in animal models of ALS demonstrated that GH administration played a protective effect on mutant SOD-1-expressing motor neurons, increasing the survival time and improving motor performance and weight loss of GH-treated transgenic mice [377]. On the other hand, it has been shown that in animal models the intra-hippocampal injection of the hormone improves spatial cognition [378] as well as learning and memory in AD-like rats [379]. Therefore, a possible usefulness of hGH in AD has been recently postulated [380]. It is possible that the time at which hGH administration is given in relation to the development of AD may play a significant role in the results obtained. In fact, GH has been shown to prevent age-induced reduction in the expression of some components in rats, including cytochromes b and c of the mitochondrial respiratory chain [381, 382].

II - Melatonin (MT) in HNDDs

Cell death and survival are known to be critical events for the evolution of neurodegeneration [35], while mitochondria being increasingly seen as an important determinant of both processes. Indeed, mitochondrial dysfunction is considered to be a major etiopathogenic factor in Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) [383]. The mechanisms thought to be involved in impaired mitochondrial function include

increased free radical generation, enhanced mitochondrial inducible NO synthase activity and NO production, pH changes, a disrupted electron transport system and mitochondrial permeability transition [39, 383, 384]. Furthermore, the CNS is very sensitive to oxidative stress, which is considered to be a key factor in the pathophysiology of neurodegenerative disorders.
Melatonin (MT) has been shown to be effective in preventing the oxidative stress/NO stress-induced mitochondrial dysfunction seen in experimental models of AD, PD and HD [383]. This hormone has unique biochemical properties such as scavenging of hydroxyl, carbonate, alkoxyl, peroxyl and aryl cation radicals and stimulation of the activities of important antioxidative enzymes like glutathione peroxidase and superoxide dismutase and can suppress nitric oxide synthase. For all these reasons it may have an important role in the treatment of HNDDs [384].
Therefore, recent studies have considered the potential clinical role of MT in the main HNDDs like AD, PD, ALS and multiple sclerosis (MS). In mouse models of AD, a significant clinical improvement with chronic MT treatment at daily dosages of 10 mgr/kg/day was obtained [385], with improvement of cognition and memory and reduction of the deposits of Aβ [386]. Most recent data on ALS patients indicate that high doses of MT can be useful in delaying the progression of this fatal disease. Importantly, MT also appears to be most beneficial in other neurovascular diseases like the highly invalidating Horton's disease ("cluster headaches) when used in high pharmacological doses, from 50 to 350 mgr/day, or even higher dosages, similar to how it has been used in patients with ALS [387, 388]. Similar beneficial effects have been recently described in an animal model of sporadic AD (OXYS rats). In this situation, early treatment with MT induces a decrease of amyloid-β1-42 and amyloid-β1-40 levels in the hippocampus and of amyloid-β1-42 levels in the frontal cortex [389]. In addition, treatment of OXYS rats with this hormone slowed down the increase in anxiety and deterioration of reference memory typical of AD [389]. These properties make this hormone unique for protecting the organism against the oxidative stress by inducing a reduction in the oxidative damage which, as above described, is considered as a key factor in the etiopathogenesis of HNDDs [383, 390]. In summary, MT administration at pharmacological dosages should be considered a promising adjuvant treatment of certain HNDDs.

III - Melatonin (MT) as an oncostatic and cytotoxic agent.

It is known that MT is produced not only at the pineal level but in all the cells of any living organism, vegetables and unicellular organisms included, where it plays a key role in maintaining normal cellular homeostasis, most likely by regulating cell oxidative metabolism [391, 392]. Some effects of MT on cellular homeostasis also seem to be strong in cancer cells showing a metabolic profile consistent with aerobic glycolysis (Warburg effect, increased glucose uptake, LDH activity, lactate production and HIF-1α activation). Here, MT is able to revert this metabolic profile inducing cytotoxicity, while in cancer cells where the Warburg effect is not seen it inhibits proliferation [393]. Finally, the differential regulation of metabolism by MT could also explain why the hormone is harmless for a wide spectrum of normal cells and a minority of malignant cells while it kills specific tumor cell types [394, 395].
These effects of MT on cancer could be surprising since the hormone has been considered for some time as a simple synchronizer between the organism and the environment. MT also behaves as an oncostatic agent [396]. At both physiological and pharmacological doses, MT has been shown to be effective in suppressing

neoplastic growth in a variety of tumors like melanoma, breast, prostate, ovarian and colorectal cancer [393, 397, 398]. It seems that this effect is mediated by the direct augmentation of natural killer (NK) cell activity as well as the stimulation of cytokine production, for example, interleukins IL-2, IL-6, IL-12 and interferon (IFN)-gamma [397]. The same authors have suggested that the physiological surge of MT at night could be considered a "natural restraint" on tumor initiation, promotion and progression, and it has been recently advanced that disrupting circadian nocturnal melatonin rhythms promotes human breast cancer growth and resistance to chemotherapy [393]. It is therefore logical that MT is increasingly becoming an adjuvant therapy in some human malignancies, even preventing adverse side-effects produced by chemo/radiotherapy such as mucositis [399]. In summary, MT appears not only to be a protecting agent against the development of certain HNDDs but also seems to be beneficial in counteracting the progression of a number of malignant tumors. However, further clinical experience in this new area is necessary.

C) Neural and platelet-derived human growth factors (PDGFs) in the treatment of HNDDs.

These new approaches clearly open the possibility of using different human growth factors (hGFs) for neuronal protection in HNDDs, either derived from hGFs stimulation, also induced by hGH [373, 374] or derived from platelet concentrates (Figure 1). This was initially suggested by our group within the frame of a new concept that was called "*the trophic factor withdrawal syndrome"* (TFWS) [35, 36]. In this vein, it has been recently shown that intranasal delivery of platelet-derived plasma rich in growth factors (PRGF) enhances hippocampal neurogenesis and reduces neurodegeneration in an amyloid precursor protein/presenilin-1 (APP/PS1) mouse model of AD [400]. PRGF also reduces neuropathologic hallmarks and improves cognitive functions in the AD mouse model [401]. In a parallel study, these authors have shown that hGFs from PRGF preparations induce neuroprotection in rodent models of Parkinson's disease (PD) by modulating pro-inflammatory processes. In that study, the effects of PRGF as a therapeutic approach to PD were evaluated in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mouse and these effects were associated with a significant reduction in nuclear transcription factor-κB (NF-κB) activation and nitric oxide (NO), cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF-α) expression in the substantia nigra [402]. From these studies, it can be concluded that PRGF can prevent dopaminergic degeneration via an NF-κBdependent signaling process. However, in spite that some relationships between platelet-derived growth factors (PDGFs), NO production and the acid-base cellular changes in HNDDs under these therapeutic measures have been described, they are still waiting to be fully understood [35, 39, 344]. At the present time it is not known if the results of these experiments are always mediated by the stimulating effect of PRGF and/or hGH on maintaining cellular acid-base homeostasis within physiological limits, so preventing the metabolic collapse induced by cell acidification and subsequent cellular death through apoptosis or similar mechanisms (Table 1). However, some evidence seems to indicate that this can be a fundamental mechanism in preventing and/or controlling neurodegeneration (Figure 1 and Table 3) [35, 37, 38].
Finally, in spite that the possibility of stimulating tumor growth with the utilization of hGH and/or hGFs and PDGFs has been raised [36, 403-406], the extensive clinical experience already available using PRGFs in many different areas of regenerative medicine appears not to have not shown any oncogenic danger [407].

Conclusions

1) Historically, systemic acid-base balance was recognized by classic medicine as the fundamental parameter to define the general concept of homeostasis. More than a century later this concept can now be extended to the cellular level where the pH and hydrogen ion dynamics occurring in cancer and neurodegeneration are seen as deviations towards opposite ends of a biological and metabolic spectrum. Also, and for the first time, both the metabolism of cancer and HNDDs can be viewed under the same wide-ranged perspective at different levels of understanding, from both basic and clinical aspects and from etiopathogenesis to treatment.

2)The pH-centric paradigm of cancer developed in this contribution permits a deep understanding of the many faces and stages of malignant disease, from cell transformation to local growth, dissemination and the metastatic process, as a single, integrated process driven by altered acid-base regulation at different phases of evolution and development.

3) Regarding cancer etiopathogenesis and treatment, the primary aim of this H^+ ion dynamics-based approach ("the pH-centric paradigm") is to manipulate the dysregulated pH abnormal dynamics of cancer cells and tissues in order to reverse tumor growth, control local invasion and deactivate the metastatic process. These abnormal cellular pH-dynamics of cancer and its consequences can be considered a chronic allostatic failure in maintaining cellular acid-base homeostasis within physiological parameters.

4) The main therapeutic aim of the pH-centric paradigm in translational and bedside oncology is the induction of a proapoptotic selective intracellular acidification of cancer cells using different membrane-bound inhibitors of proton transport and of other non-proton transport derived cellular acidifiers. This would reverse the selective cancer proton reversal of malignant cells and tissues and consequently increase tumoral interstitial pH. At the same time, this would inhibit the Warburg effect and act as an antiglycolytic measure, thus controlling cancer growth and the metastatic process. This perspective represents a rational approach to cancer therapeutics encompassing all stages of cancer development at the same time and it has the potential of being selectively exploited in the treatment of many, if not all, malignant solid tumors and leukemias.

5) Since cancer cells use different proton pumps and transporters to protect themselves from an intracellular accumulation of hydrogen ions, it is probable that an integrated and concerted utilization of all known inhibitors of proton extrusion in pharmacological dosages will be necessary in the therapy of human malignancies. This is due to the fact that there are multiple pH regulators at the membrane of cancer cells that can be co-expressed at the same time in hostile conditions and also that the inhibition of one transporter will be compensated by the overactivation of other/s *("the neostrategy of cancer cells and tissues").*

6) For the first time, the basic to clinical approach within the field of oncology research advanced here (*translational research*) is now enriched by an interdisciplinary effort to stimulate a more outreaching vision in order to integrate within the same theoretical frame an otherwise separated area of research like neurology (*transversal research*). This wide-ranged perspective of the entire pH-related cellular homeostasis field and

metabolic spectrum offers the opportunity to significantly improve the understanding of the contradictory nature of the acid-base and energetic abnormalities underlying the pathological deregulation of cell death in these two specular processes. In this context, an intracellular pH (pHi)-related approach to these two metabolically opposed situations like cancer and human neurodegenerative diseases (HNDDs) provides a new integral model and new paradigm pointing towards a general and unified theory of the apoptosis-antiapoptosis dualistic machineries and/or cellular programmed pro-death and anti-death mechanisms.

7) One of the main aims of this contribution is to promote the new pH-centric paradigm on the therapeutic utilization of proton transport inhibitors and other non proton transport-derived intracellular acidifiers as well as drugs affecting ion channels physiopathology in human cancer.

8) Finally, we advance that the utilization of a wide array of human growth factors (hGFs) and hormones like human growth hormone (hGH) and melatonin (MT), may have an important role in the oncoming treatments of HNDDs like Alzheimer disease and that those therapeutic measures seem to be able to reverse the acidification-dependent neural toxicity and apoptosis characteristic of neurodegeneration by stimulating cellular metabolism and defending its homeostasis through the therapeutic activation of NHE1 and other membrane-bound proton transporters.

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Conflicts of Interest. The authors declare the following competing financial interests: EA is the Scientific Director and GO is a scientist at the BTI-Biotechnology Institute, a dental implant company that performs research in the fields of oral implantology and PRGF-Endoret technology. The rest of the authors declare no conflicts of interest.

Figure Legends

Figure 1

The role of human growth factors (hGFs) and growth hormone (hGH) on NHE and on cellular metabolic stimulation. The possibility of malignant transformation after treatment with hGH [403-405] or PDGF [406] has been raised but has not been shown in regenerative medicine [407]. On the contrary, lack of hGFs and/or hGH keeps levels of cell metabolism very low and induces cellular acidification and apoptosis. For more information see text and references [35, 354, 357-359, 366, 370, 373, 380].

Abbreviations: VEGF: Vaso endothelial growth factor; IGF-1: Insulin growth factor 1; FGF: Fibrobalast growth factor; PDGF: Platelet-derived growth factors; EPO: Erythropoietin; EGFR: Endothelial growth factor receptor; NGF: Nerve growth factor.

Figure 2

Effect of pH on lipids packing.

(A) Assuming a leaflet composed of charged lipids. The optimal area per lipid is determined by the competition between an attractive energy that reflects lipids attraction linked to their hydrophobic tails and a repulsion energy, which we will assume to be linked to a net charge carried by all the lipids. The competition between these two defines a minimum of energy. Note that in the figures, a_0 corresponds to the optimal distance between adjacent lipid heads.

B) Thus the minimum of energy provides the optimal distance between lipids including their optimal area in the monolayer. Note that the packing of lipids is not always defined by hard core contact/steric repulsion and that, accordingly, there is room to change this packing.

C) With regard to negatively charged lipids, an increase in the concentration of hydrogen ions allows more of them to interact with lipids' head. Thus by masking their negative charges, the long-range repulsion between lipids is disturbed. The resulting effect will be an alteration of the positioning of the minimum energy, which will move closer to the lipids.

D) Top view of a portion of a membrane. The lipid's hard core head is colored in red and the optimal area per lipid driven by repulsive/attractive interactions, is drawn in blue. Changes in pH are expected to redefine the optimal area per lipid and thus their packing. In the figure, a decrease in the pH is represented. In conclusion, a low cytosolic pH is expected to decrease the surface area per lipid (Modified from Rauch [176]).

Figure 3

General scheme showing some shared aspects of the role of altered intracellular pH (pHi) and extracellular pH (pHe) and ion channels in cancer, brain ischemia and HNDDs.

Alterations in both intracellular (pHi) and extracellular (pHe) pH are tightly involved regulating cancer progression and cell death in both brain ischemia and HNDDs (see text for details). In cancer cells, protons (H^+) produced by the glycolytic metabolism are extruded by Na^+/H^+ exchanger (NHE1) and/or other membrane-bound proton transporters and the voltage-gated proton channel, Hv1 [292-296]. The activity of

NHE1 is enhanced by voltage-gated sodium channels that are abnormally expressed in cancer cells [260, 261, 305], as well as by increases in the intracellular Ca^{2+} concentration, which is regulated by the Na^{+}/Ca^{2+} exchanger (NCX) activity [140] with the participation of numerous Ca^{2+}- permeable channels also up-regulated in cancers [279]. Both the increase in intracellular pH (pHi) and the decrease in extracellular pH (pHe) drive cancer processes such as transformation, proliferation, survival, migration, and ECM proteolysis/invasion. The opposite situation takes place in both ischemia and HNDDs where the low pHi of cells in either condition can be secondary both to an intracellular acidosis of a metabolic origin (metabolic/aerobic acidosis) and/or to acidosis related to a lack of oxygen (hypoxic/anaerobic acidosis). This is associated with the over-activation of acid-sensing ion channels (ASICs), [272, 326-329] in ischemia [318-322] and in HNDDs, with glutamate ionotropic receptors (AMPA and NMDA receptors) generating Ca^{2+} overload [310, 315-317] and neuronal cell death [36-39, 271, 342-344]. For further details see text.

Abbreviations: Nav1.5: Voltage-gated sodium channel isoform 1.5; NHE1: Na^{+}/H^{+} exchanger type 1; NCX: $Na^{+}/Ca2^{+}$ exchanger; ASIC1a: Acid-sensing Ion channel type 1a; Hv1: Voltage-gated proton channel type 1; HNDDs: human neurodegenerative diseases; AMPA-R: (α-amino-3-hyroxil-5-methyi-4-isoxazolepropionic acid receptor); NMDA-R: (N-methyl-D-aspartate receptor); GFRs: Growth Factor Receptors.

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